EXPERIMENTAL STUDIES ON THE COOLING IRRIGATION OF CEREBRAL VENTRICULAR SYSTEM (I)

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by

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INTRODUCTION

Many experiments about the intraventricular injection with various medicaments have so far been performed for various purposes. Particularly cardiotonica, autonomotropic drugs, hormones, vitamines or blocking agents (chlorpromazine) have been injected into the cerebral ventricle for the purpose of the therapeutic attempt. On the other hand, dye stuffs, fluorescent substances, iodide, bromide, thiocyanate and radioisotopes have also been employed intraventricularly or intracisternally for the investigation of secretion and absorption of cerebrospinal fluid.

In 1952, the ventricular irrigation from the lateral ventricle to the major cisterna with warm physiological saline solution and some autonomotropic drugs was attempted by UEDA and his coworkers on 23 patients with schizophrenia, expecting certain therapeutic effect [17].

TAKEUCHI reported some beneficial effects of the cooling irrigation of ventricular system on some animals and a patient with hyperthermia due to tuberculous meningitis. [16]

The cooling irrigation between the lateral ventricle and major cisterna with cold RINGER's solution was performed systematically on adult dogs in our laboratory. Consequently some interesting facts such as the effect on the responsiveness of animals were confirmed in the result of hypothermia to the localized nervous tissue near the ventricular wall. In this paper, these physiological changes in animals are described.

METHOD

Throughout the experiments adult mongrel dogs of 4 to 12.5 kg in weight were used. Under the basic anesthesia with thiopental sodium a round burr hole about 1.5 cm of diameter was trepanated in the parietal skull through the cutaneous incision on the midline.

The dura mater was electrically coagulated in order to adhere with the arachnoid, pia and cerebral cortex around the ridge of burr hole on the skull (by this adhesion irrigating fluid should not be allowed to flow into the subarachnoidal space). Then the dura was incised, and cerebral substance was dug towards the lateral ventricle with small spatulae (5 mm in width).

The opening of the ventricle was confirmed by springing of cerebrospinal fluid and direct vision of white shiny internal wall of the ventricle.

Through the incised spatium a NELATON's catheter of No. 6 or 7 was inserted into the ventricle, and a piece of spongel (foamed gelatin) was plugged up around the catheter over the cortex in order to prevent the counter current of irrigating fluid from the incised hole of brain matter. Temporal muscles were firmly sewed together, and the inserted catheter fixed on a part of sutural line was used for the inflow of irrigating fluid.

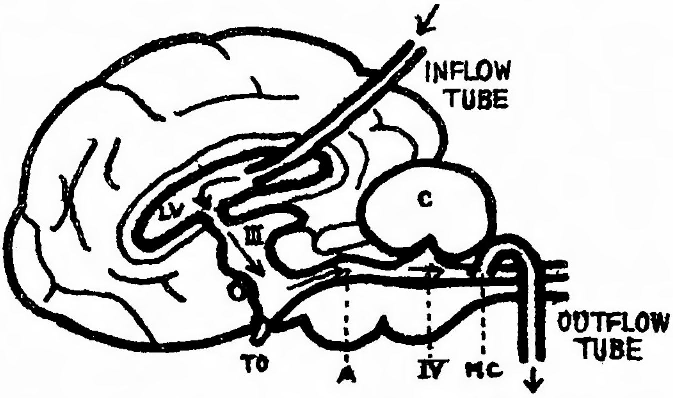

Fig. 1 An illustration of the irrigating mechanism. The inflow tube is inserted into the lateral ventricle and outflow tube is put in the major cisterna. The flowing way of irrigating fluid from the lateral ventricle, through the third ventricle, aqueduct of SYLVIUS, and fourth ventricle, to the major cisterna is indicated as arrows.

A, indicates aqueduct; C, cerebellum; LV, lateral ventricle; MC, major cisterna; TO, tractus opticus; III, third ventricle; IV, fourth ventricle.

On the other hand, muscles of the nape were separated on the midline, and the dura of major cisterna was exposed under suboccipital craniotomy, while the atlas was gnawed away if necessary. The major cisterna was opened, and a NELATON's catheter of No. 8 to 10 was inserted into the cisterna and fixed on the muscles of the nape in situ, then muscles were sewed together closely around the inserted catheter which was used for outflow.

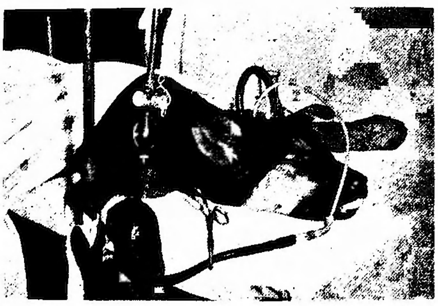

Fig. 2 An appearance of the completed irrigating mechanism. The anterior fine tube inserted into the lateral ventricle and the posterior thick tube put in the major cisterna. The inflow tube is connected to irrigator.

When this mechanism of ventricular irrigation was completed, dog became half awake. In this state dog responded promptly as barking and struggling against the pinching of his nose, but quietly laid unless he was stimulated. Remaining of the anesthesia in this grade was rather convenient to proceed the following experiment. The irrigator hanged upon suitable height was filled up with irrigating fluid (physiological saline solution was used in the earier experiments, but later used only the RINGER's solution for the reason as followed). The inflow tube was connected with the irrigator, and then irrigating system from the irrigator to the outflow tube through the ventriclar system was completed (Fig. 1 and 2).

There would been no resistance in the passage of fluid with the adequate speed of irrigation (in the range of about 20 to 30 cc per minute) under this completely performed experimental mechanism. The speed of irrigation could be controlled easily, i. e. the higher the irrigator hanged, the greater the speed of flow became.

A stop-cock which inserted on a way to the inflow tube was also useful for this control. It was proved that, morever, there was no by-pass of the irrigating fluid through the subarachnoidal space. Fig. 3 & 4 show the parietal and medial aspects of the brain of dog in which diluted methylen blue solution was irrigated under the same condition as like as the cooling ventricular irrigation, for the purpose of staining of the path way of irrigating fluid, and the staining of only the ventricular system is verified.

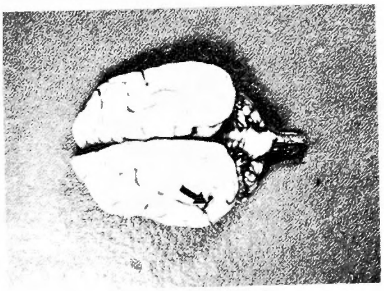

Fig. 3 A parietal view of the brain in the dog irrigated on usual method with methylen blue. The arrow in the lefthemisphere indicates the inserted site. No invasion of irrigated fluid into the subarachnoidal space surrounding surface of the cerebral hemisphere is shown.

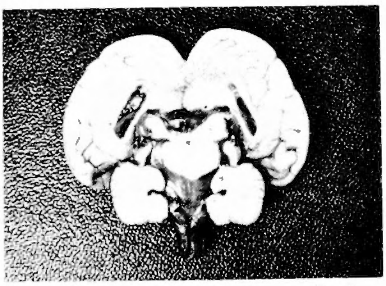

Fig. 4 A medial view of the brain in the dog irrigated on usual method with methylen blue. Only the ventricular system is stained by dye.

As soon as the condition of dogs became adequate to the main experiment after the awaking from anesthesia, pre-experimental data were recorded and irrigation was set out.

The clamp of the inflow tube was removed and cooled fluid was set out to irrigate from the inflow tube. The temperature of outflowed fluid, state of consciousness, rates of respiration and puls, and blood pressure were recorded every 30 to 60 seconds throughout the experiment. The state of consciousness was mainly judged from the "nose pinching test" which was tested by pinching his nose with Kocher's clamp. In addition, blinking reflex (reflex of orbicularis oculi), corneal reflex, and size of pupils were also examined. Blood pressure in the femoral artery was measured directly by the U-formed column of mercury.

RESULTS

In this experiment 49 adult dogs were used. In the earlier stadium of experiment, on six dogs tubocurarine chloride was employed for the facilitation of preparatory operation instead of the basic anesthesia with thiopental sodium. But all of them died soon after the intravenous injection of vagostigmin, which was used in order to eliminate the excessive effect of tubocurarine chloride. Thus the basic anesthesia with thiopental sodium was employed on 40 dogs excepting of three ones. On 15 dogs experiments were failed according to the failure of intubation into the lateral ventricle or injuring of the thalamus and medulla oblongate. On 9 of the other 28 dogs, in which the succesful irrigating mechanism was performed, physiological saline solution was used as irrigating fluid, and on 19 dogs Ringer's solution was used.

(1) IRRIGATION WITH COLD RINGER'S SOLUTION

Following results are based on the observations of 15 dogs in 29 experiments,

Table 1 — Irrigating Conditions and Results of the Cooling Ventricular Irrigation with RINGER's Solution.

Dog No.	Sex	Body Weight (kg)	Conditions of Irrigation				Changes during Irrigation									After Cessation of Irrig.				Incidents	Other Notions
							Existence and Time Lapse Taken Before Disappearance of Responses (sec.)									Time Lapse Taken Before Appearance of Responses (sec.)					
			Speed of Flow (cc/min.)	Duration (min.)	Temp. of Inflowed Fluid (℃)	Temp. of Outflowed Fluid (℃)	Nose Pinching Response	Blinking Reflex	Corneal Reflex	Light Reflex	Respiration Rate	Pulse Rate	Blood Pressure	Size of Pupils	Muscle Tonus	Nose Pinching Resp.	Blinking Reflex	Corneal Reflex	Light Reflex		
7	♀	12.5	27	14.5	12	23	20	20	90	Weakened	Decreased	Unchanged	–	Enlarged	Relaxed	30	30	30	–		
〃	〃	〃	27	15	10	22	15	90	120	Weakened	Decreased	Decreased	–	Unchanged	Relaxed	150	30	30	–		
20	♂	7	20	9.5	11.8	20.5	30	30	–	Unchanged	Decreased	Decreased	–	Reduced	Relaxed	30	19	–	–	Hypersalivation	
21	♂	6	16	5	11.5	21	15	120	–	Unchanged	Decreased	Decreased	–	Reduced	Relaxed	37	13	–	–		
22	♂	6	22~26	11	13	21	30	30	–	Weakened	Increased	Decreased	–	Reduced	Relaxed	14	14	–	–		
24	♂	9	8~16	22	9	27	Weakened	Weakened	–	Unchanged	Increased	Unchanged	–	Unchanged	Unchanged	–	–	–	–		
〃	〃	〃	30	12	13	24	360	Weakened	–	Weakened	Increased	Unchanged	–	Reduced	Relaxed	60	–	–	–		
25	♂	11	30	10	15	24	510	Weakened	510	Weakened	Unchanged	Increased	–	Reduced	Unchanged	7	–	15	–		
〃	〃	〃	50	3	11.8	19	18	Weakened	–	Weakened	Increased	Decreased	–	Enlarged	Relaxed	10	–	–	–		
〃	〃	〃	28	3	15	28	90	Weakened	–	Weakened	Decreased	Decreased	–	Unchanged	Relaxed	21	–	–	–		
26	♂	10	36	4	15	24	15	Weakened	150	Weakened	Decreased	Decreased	–	Reduced	Relaxed	10	–	30	–		
〃	〃	〃	28	3.5	9.5	23.5	30	30	30	Unchangde	Ceased	Decreased	–	Unchanged	Relaxed	15	15	15	–	Apnoea, Arrhythmia	
〃	〃	〃	40	3.5	11	24	10	Weakened	Unchanged	Weakened	Ceased	Decreased	–	Reduced	Relaxed	60	40	–	–	Apnoea, Arrhythmia	
28	♀	12	26	3.5	14	–	50	150	20	Unchanged	Ceased	Unchanged	Lowered	Unchanged	Relexed	120	60	–	–	Apnoea,	
〃	〃	〃	26	3.5	9	26	15	90	–	Unchanged	Ceased	Decreased	Lowered	Unchanged	Relaxed	–	–	–	–	Apnoea	Died from Anoxia
30	♂	10	20	5	10	27.5	Weakened	Unchanged	Unchanged	Unchanged	Unchanged	Uuchanged	Lowered	Unchanged	Unchanged	–	–	–	–		
〃	〃	〃	24	10	7	21.5	Weakened	Unchanged	Unchanged	Unchanged	Unchanged	Decreased	Lowered	Unchanged	Unchanged	–	–	–	–		
〃	〃	〃	30	4	10	22.8	17	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Lowered	Unchanged	Relaxed	5	–	–	–		
31	♀	4	34	8	11	24	150	300	240	Unchanged	Increased	Decreased	Lowered	Reduced	Relaxed	30	10	10	–		
35	♂	7.5	16~24	11	9.2	19.5	25	30	30	Unchanged	Unchanged	Decreased	–	Reduced	Relaxed	24	15	15	–		Without Thiopenthal
36	♀	9	44	7.5	7	15.2	45	Weakened	145	Weakened	Decreased	Decreased	–	Reduced	Relaxed	30	–	40	–	Transient Nystagmus Arrhythmia Hypersalivation	Without Thiopenthal
〃	〃	〃	34	7	12	16.5	45	120	120	Weakened	Decreased	Decreased	–	Reduced	Relaxed	20	30	20	–	Transient Nystagmus	Without Thiopenthal
〃	〃	〃	24~34	7	12	17.2	13	Weakened	60	Unchanged	Decreased	Increased	–	Reduced	Relaxed	10	–	20	–	Transient Nystagmus	Without Thiopenthal
37	♂	7.5	32	7.5	7	18	Weakened	Weakened	90	Unchanged	Unchanged	Increased	–	Reduced	Unchanged	–	–	15	–	Transient Nystagmus after Cessation of Irrig.	Without Thiopenthal
〃	〃	〃	34	9	7	16	150	180	60	180	Decreased	Increased	–	Reduced	Relaxed	15	20	15	15	Transient Nystagmus after Cessation of Irrig.	Without Thiopenthal
38	♂	9	23	11	9	22	60	30	–	–	Decreased	Unchanged	Unchanged	–	Relaxed	30	30	–	–		
〃	〃	〃	21~39	9	9	17	30	60	–	–	Decreased	Decreased	Lowered	–	Relaxed	20	20	–	–		
39	♀	8	13~22	11.5	7	17	18	300	300	Unchanged	Ceased	Decreased	Lowered	Reduced	Relaxed	20	40	20	–	Apnoea	
〃	〃	〃	23	15	7	15.5	30	60	–	–	Ceased	Decreased	Lowered	–	Relaxed	–	–	–	–	Apnoea	Continued The Cooling Irrig. under Artificial Breathing

Note: Numerals in the Columns of each reflexes indicate the time lapse taken before disappearance of responses in unit of second. In the respiration and the puls rate, those have been increased more than 10 times in a minute as compared with the state before irrigation are described at "Increased", reduced less than 9 times in a minute "Decreased" and varied within 9 times in a minute "Unchanged". In the blood pressure, those have been elevated or lowered over the range of each 20 mm Hg as compared with the level before the irrigation are described at "Elevated" or "Lowered" and varied within each 19.0mmHg "Unchanged". These notions are also applicable to following tables (2~5).

Dog No.	Sex	Body Weight (kg)	Speed of Flow (cc/min.)	Duration (min.)	Temp. of Inflowed Fluid(℃)	Temp. of Outflowed Fluid(℃)	Changes during Irrigation								Incidents	Other Notions
							Nose Pinching Resp.	Blinking Refex	Size of Pupils	Light Reflex	Respiration Rate	Pulse Rate	Blood Pressure	Muscle Tonus		
7	♀	12.5	18	3	38	37	Unchanged	Unchanged	Unchanged	Slightly Weakened	Unchanged	Unchanged	–	Unchanged	none in all cases	
20	♂	7	12	7.5	36	35	Unchanged	Unchanged	Unchanged	Slightly Weakened	Unchanged	Unchanged	–	Slightly Relaxed		
21	♂	6	24	5	38.5	37	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	–	Unchaged		
22	♂	6	28	5	37	37	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	–	Unchanged		
31	♀	4	34	8	36	34	Uuchanged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Uncdangeh		
36	♂	9	30	7	36	34	Unchanged	Unchanged	Slightly Enlarged Only Oposite Side.	Unchanged	Unchanged	Unchanged	–	Unchanged		Without Thiopenthal Sodium
37	♂	7.5	34	6	39	36	Unchanged	Unchanged	Reduced	Unchanged	Unchanged	Unchanged	–	Unchanged		Without Thiopenthal Sodium
38	♂	9	37	9	38	36	Unchanged	Unchanged	Unchanged	Unchanged	Decreased	Decreased	Unchanged	Unchadnge		

Table 3 — Irrigating Conditions and Results of the Ventricular Irrigation with Hot Ringer's Solution (Control).

Dog No.	Sex	Body Weight (kg)	Conditions of Irrigation				Changes during Irrigation										Incidents
			Speed of Flow (cc/min.)	Duration (min.)	Temp. of Inflowed Fluid(℃)	Temp. of Ouflowed Fluid(℃)	Nose Pinching Resp.	Blinking Reflex	Corneal Reflex	Size of Pupils	Light Reflex	Respiration Rate	Pulse Rate	Blood Pressure	Muscle Tonus		
41	♂	12	15	8	43	35	Unchanged	Unchanged	Unchanged	Unchanged	Weakened	Increased	Decreased	–	Unchanged		
〃	〃	〃	20	8	46	36.5	Unchanged	Unchanged	Unchanged	Enlarged	Unchanged	Unchanged	Decreased	–	Unchanged		Arrhythmia
45	♂	8	10	8	45	34.5	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Increased	Increased	Unchanged	Unchanged		
48	♂	8	10	8	47	38	Unchanged	Weakened	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged		
50	♀	6	26	8	47	41	Unchanged	Unchanged	Unchanged	Enlarged	Unchanged	Ceased	Decreased	Elevated	Unchanged		Apnoea

Table 4 — Conditions and Results of the Cooling Ventricular Irrigation with Physiological saline Solution.

Dog No.	Sex	Body Weight (kg)	Conditions of Irrigation				Changes during Irrigation							Incidents	Other Notions
			Speed of Flow (cc/min.)	Duration (min.)	Temp. of Inflowed Fluid(℃)	Temp. of Outflowed Fluid(℃)	Nose Pinching Resp.	Blinking Reflex	Size of Pupils	Light Reflex	Respiration Rate	Pulse Rate	Muscle Tonus		
9	♂	6	5	5	14	31	Disappeared	Disappeared	Enlarged	Disappeared	Increased	Increased	Relaxed		
10	♂	8	20	5	13	27	Disappeared	Weakened	Enlarged	Unchanged	Decreased	–	Stiffened	Progressive Gross Shiverring	
11	♂	8	7	5	5	27.5	Unchanged	Unchanged	Enlarged	Unchanged	Unchanged	–	Unchanged	Nystagmus	Wagged His Tail Continuously
12	♂	10	25	5.5	10	–	Disappeared	Disappeared	–	Unchanged	Decreased	Unchanged	Stiffened	General Convulsion	Barked and Elected His Tail Continuously
16	♀	7	8	10	12	33	Disappeared	Disappeared	Unchanged	Unchanged	Increased	Increased	Relaxed		}Delayed Awakening
〃	〃	〃	8	6	10	34	Disappeared	Disappeared	Unchanged	Unchanged	Decreased	Increased	Slightly Relaxed		
17	♂	11.5	30	11	21	30	Disappeared	Disappeared	Enlarged	Unchanged	Decreased	Decreased	Stiffened	Oculomotor Palsy, Nystagmus, Convulsion in upper Part of Body	
18	♀	7.5	30	5	14.5	32	Disappeared	Weakened	Enlarged	Unchanged	Increased	Decreased	Unchanged	Gross Shiverring	

Table 5 — Conditions and Results of the Ventricular Irrigation with Warm Physiological Saline Solution (Control).

Dog No.	Sex	Body Weight (kg)	Conditions of Irrigation				Changes during Irrigation							Incidents
			Speed of Flow (cc/min.)	Duration (min.)	Temp. of Inflowed Fluid(℃)	Temp. of Outflowed Fluid(℃)	Nose Pinching Resp.	Blinking Reflex	Size of Pupils	Light Reflex	Respiration Rate	Pulse Rate	Muscle Tonus	
8	♀	8	10	13	38	–	Unchanged	Unchanged	Enlarged	Unchanged	Increased	Increased	Stiffened	
9	♂	6	5	5	34	36	Disappeared	Unchanged	Enlarged	Unchanged	Unchanged	Increased	Relaxed	
10	♂	8	8	10	37	37	Unchanged	Unchanged	Enlarged	Disappeared	Increased	Unchanged	Stiffened	
11	♂	8	17	30	38	35	Unchanged	Unchanged	Unchanged	Unchanged	Increased	Increased	Unchanged	Conjugate Deviation
12	♂	10	30	19	37	37	Weakened	Unchanged	Enlarged	Weakened	Increased	Unchanged	Slightly Relaxed	Hypersalivation
17	♂	11.5	15	5	36	37	Temporarily Disappeared	Unchanged	Enlarged	Disappeared	Decreased	Decreased	Slightly Relaxed	Oculomotor Palsy
20	♂	7	10	9	36	37	Disappeared	Unchanged	Remarkably Enlarged	Disappeared	Decreased	Increased	Unchanged	Hypersalivation Exophthalmus Nystagmus

in which only the cold RINGER's solution was used for the ventricular irrigation (Table 1).

1. CONDITIONS OF IRRIGATION.

a) *Basic anesthesia* : Dogs had been slightly anesthetized with the intravenous administration of thiopental sodium of 30 mg per kg body weight for the intubating into the ventricular system as described above, and the irrigation was set out after their awakeness from anesthesia.

Under the local anesthesia with procaine hydrochloride the cooling irrigation was also performed at six times on three dogs in order to shut out the effect of thiopental (D. 35, 36, 37), while the results were as same as those of the cases anesthetized by thiopental sodium except only one. In this exceptional case the more intense cooling was necessary for the introduction into unresponsiveness, and the restoration from the unresponsive state after the cessation of irrigation was more rapid than in other cases.

b) *Speed of irrigation* : Irrigation-flow was able to be controlled by means of the changing of fall height and the adjustment of the stopcock of irrigator. The speed of flowing of 30 cc. per minute was enough to aquire the unresponsive state of animals, while the cooler the irrigating fluid was, the slower the speed of irrigation required for the induction of unresponsive state was. When the speed of irrigation was accelerated, the temperature of outflowed fluid from the major cisterna was generally reduced and the effect of ventricular cooling was strengthened. So far as such a grade of the flow of fluid was furnished, mechanical effects against the internal wall of the ventricles would be negligible.

c) *Duration of irrigation* : Duration of the cooling irrigation was 8.5 minutes in average, varying from 3 to 22 minutes. In such a short duration the observation of changes in general condition during the irrigation was possible enough because of the extreme rapidity of appearance and disappearance of the unresponsive state, while this short unresponsive state may not be called "anesthesia".

One case, on which the cooling irrigation was continued as long as 30 minutes (D. 23), suggested the possibility to be prolonged the duration of irrigation without the reduction of flow due to acute carebral edema, but this case was excluded from Table 1 because of the lack of decided observation of the changes in consciousness during the irrigation.

From this experiments it may be conceivable that the too long duration of irrigation should be resulted in cerebral edema, elevation of intraocular pressure and tendency to exophthalmus on the irrigated side. It was proved that the restoration of cerebral temperature required five to ten minutes following the cessation of irrigation. Therefore the interval of 15 to 20 minutes should be allowed for the successive irrigations on a same dog.

d) *Temperature of irrigating fluid* : The temperature of inflowing fluid was measured immediately before the inflow into the ventricle at the point of connection between the tube from irrigator and NELATON's catheter which was inserted into the lateral ventricle. The temperature of inflowing fluid measured at the point above mentioned was varied in the range of 7° C to 15° C, in average, 10.5° C, while that of the outflowed fluid was 15.2° C to 28°C, in average 21.3° C. Measuring of the temperature of inflowing fluid was carried out immediately before and after the irrigation, while that of outflowed fluid was measured every one minute during the irrigation.

Regarding as the temperature of outflowed fluid certain relationship with the appearance of unresponsiveness was comfirmed. To clarify this relation, the fluids of various temperature were used, and it was proved that there was a certain threshold in the temperature of irrigating fluid for the appearance of unresponsiveness. The temperature of this threshold was 25° C, and the consummate unresponsiveness was not obtainable in some cases beyond this threshold as shown in Fig. 5. In this figure, D. 24 & 30 were the cases on which it was impossible to completly abolish the nose pinching response, because of the higher temperature of outflowed fluid than the threshold.

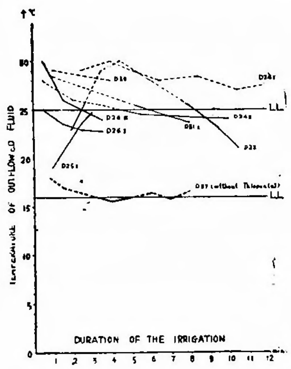

Fig. 5 Showing the relation between temperature of the irrigating fluid and obtainable unresponsiveness. The broken lines indicate the unextinguishable or weakened nose pinching response. The solid lines represent the abolished response.

On the cases without thiopental, this threholds was more lower than that on the cases with basic anesthesia : i. e. 16° C (Fig. 5).

2. RESPONSIVENESS UPON THE STIMULATION FROM OUTSIDE.

The responsiveness upon the stimulation from outside was examined by the nose pinching test and tests of blinking and corneal reflex. These reflexes were diminished in the order above described following the setting out of the cooling irrigation.

a) Nose pinching response: Our "nose pinching test" is a test of escape-reflex. The procedure of this test is as followed: the wing of nose, the most sensitive part in the face of dog, is pinched by the tip of Kocher's clamp. Following this stimulus dog in the normal state cries out, twitches his facial muscles and struggles wagging his limbs and tail. The application of slight basic anesthesia did not so remarkably inhibit this response. As it was seemed that this test might be the most simple and exact, the effect of cooling irrigation on the consciousness was examined by this test.

The nose pinching response was abolished so rapidly in almost all cases so far as the cooling irrigation was performed under the adequate condition.

In our 29 experiments, the abolishment of this response was recognized in 25 cases (86.6%), and in the other four cases (13.4%) it was able to be weakened this response. In three of these insufficient cases the temperature of outflowed fluid was not reached to the threshold which has been described above, and in the other one it was failed to abolish this response in spite of the suitable condition of irrigation, while the cause was not yet clarified.

In 16 of 25 cases followed by the succesful results, this response was abolished within 30 seconds after the beginning of irrigation, and in three cases within 31 to

60 seconds, in seven cases within 61 to 150 seconds, in the other two cases it was required for 6 and 8.5 minutes respectively before the abolishment of this response. It may be worthy of attention that the disappearance of escape-reflexes took place in almost all cases within such a brief interval as 40 seconds in average, and the recovering interval from unrespontive state after the cessation of irrigation was also remarkably short, i. e. 33.4 seconds in average. Recovering of this response within the interval of 10 seconds was recognized in five cases. There was no case in which the abolished response was not recovered following the cassation of irrigation (Table 1).

b) *Blinking reflex* : This is a defense reflex which is provokated by touching the eye-lid, and disappearance of this reflex may be used as a indication of unresponsiveness.

In 16 (55.2%) of 29 cases this reflex was disappeared, in 10 cases (34.5%) weakened (A group), and in three cases (10.3%) unchanged throughout the all duration of cooling irrigation (B group).

In A group the lapsed time from the beginning of irrigation to disappearance of this reflex was longer than that of nose pinching response, while it varied from 20 sec. to 5 min., in average 106.2 seconds.

In B group, two cases were the same ones in which the nose pinching response could not be abolished, and in the other one the corneal reflex remained unchanged in spite of the abolishment of the nose pinching response (Table 1).

c) *Corneal reflex* : Disappearance of the corneal reflex was verified in 14 (77.8 %) of 18 cases, while in four cases (22.2%) it was not verified. The lapsed time from the beginning of irrigation to disappearance of this reflex was longer than that of the nose pinching response and blinking reflex, while it varied from 20 sec. to 8.5 min., 140.4 seconds in average, and this reflex was disappeared simultaneously with the blinking reflex in most cases. In two of four cases in which this reflex did not disappear, another reflexes were not also abolished, while in the other two cases the nose pinching response was only abolished (Table 1).

3. CHANGES ON PUPILS

a) *Size* : In 15 (57.7%) of 26 cases the sizes of pupils were reduced, in nine (34.6%) unchanged, and in two rendered to be mydriatic (Table 1). As to the pathophysiological genesis of such myosis and mydriasis full information is still lacking, while in the control experiments performed with use of the warm fluids only few changes in the size of pupils were observed (Table 2).

Sizes of the myotic pupils in the cases being irrigated with Ringer's solution were almost as slight as one to two mm, and the variation of them was not greater than that of the mydriatic pupils in the cases being irrigated with physiological saline solution.

b) *Light reflex* : This reflex was remained almost unchanged throughout all duration of the cooling irrigation, while in only one (3.8%) of 26 cases disappearance of this reflex was observed, weakened in 10 cases (38.5%), and unchanged in the others (57.5%) (Table 1).

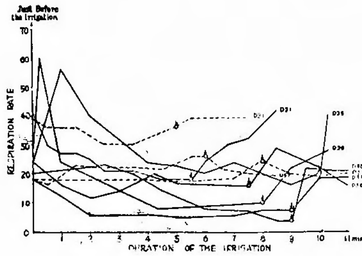

Fig. 6 Changes in the respiration rate which were observed on typical courses during the ventricular irrigation. Solid lines indicate those which were irrigated with cold RINGER's solution. Broken lines indicate those with warm solution. Circles with arrows represent the stopping points of the irrigation.

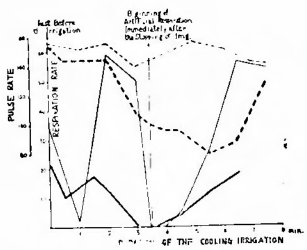

Fig. 7 Changes in the pulse rate during the respiratory paralysis occurring in the course of the cooling ventricular irrigation. Two cases are showed as representation in this series of animals. Broken lines indicate the pulse rate. Solid lines represent the respiration rate. The thick lines: D26, the narrow lines: D28.

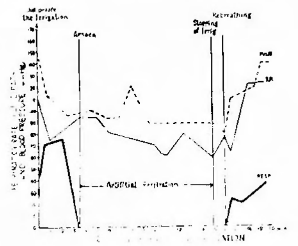

Fig. 8 Relation between the pulse rate and the blood pressure during the respiratory paralysis which occured in the course of the cooling ventricular irrigation with employment of artificial respiration.

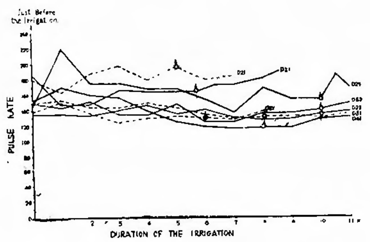

Fig. 9 Changes in the pulse rate during the ventricular irrigation with cold RINGER's solution(solid lines), and with warm RINGER's solution (broken lines). The circles with arrows indicate the stopping points of the irrigation.

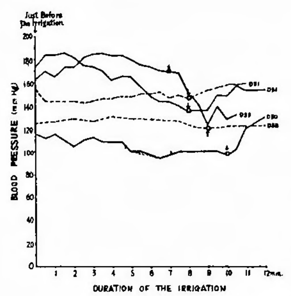

Fig. 10 Canges in the blood pressure during the ventricular irrigation with cold RINGER's solution (solid lines), and with warm RINGER's solution (broken lines). The circles with arrows indicate the stopping points of the irrigation.

4. RESPIRATION

Changes in the respiration were so remarkable, possibly following to the direct cooling effect on the respiratory center in medulla oblongata, that the reduction of respiration rate was recognized in 20 (68.3%) of 29 cases. (I provide the rate which had reduced less than 10 per minute to "reduction" as compared with the state before cooling irrigation). In four cases (13.8%) the rate increased (more than 10 per minute), and in the other five cases (17.9%) unchanged (varied within 9 in a minute (Table 1).

Typical respiratory reduction in six cases and data of controls were shown in Fig. 6. The respiration rate was rapidly reduced within several minutes after the beginning of cooling irrigation, while the initial increase in respiration rate was observed in some cases with the deepened breathing about 30 minutes after the beginning of irrigation. Following the cessation of irrigation, respiration rate was recovered to the same state as before the irrigation with a temporary increase within two to three minutes.

In six cases the cooling irrigation was carried out too vigorously to arrest the respiration, while this apnoea could be restored and animals breathed normal deep respiration soon after the cessation of irrigation followed by the application of artificial respiration (Fig. 7).

Another case in which the artificial respiration was applied immediately after the arrest of respiration showed no remarkable changes in the general condition, pulse rate and blood pressure in spite of so much vigorous cooling irrigation as former cases (Fig. 8).

5. PULSE RATE

In 18 (62.1%) of 29 cases, pulse rate was decreased (less than 20 per minute from the level before irrigation), while in four cases (13.8%) increased (more than 20 per minute from the level before irrigation) and in seven cases (24.1%) unchanged (shifted within 19 per minute) (Table 1). In all cases a tendency of the reduction of pulse rate was observed, but the grade of reduction was slighter than that of respiration rate (Fig. 9).

Recovery of pulse rate after the cessation of irrigation needed longer time than that of respiration rate, and it was more than three minutes in most cases. Arrythmia was occasionaly observed in such cases with the arrest of respiration, while they disappeared spontaneously as soon as the respiration had recovered.

6. BLOOD PRESSURE

In nine (90%) of ten cases, fall of blood pressure was also observed in the range of less than 20 mm Hg. from the level before irrigation, while in only one case almost unchanged (fall within 19 mm Hg.) (Table 1 & Fig. 10). Most of them showed an initial elevation, and after the lapse of 6～7 minutes blood pressure gradually fell to minimum level, while a time lapse demanding for recovering to the level before experiment was as blief as 1～2 minutes.

7. CHANGES IN THE RECTAL TEMPERATURE

Rectal temperature was measured in six cases, and in the half of them it was decreased in the range of 0.2° C to 0.5° C, while no change in the others. Initial elevation varying from 1.3° C to 0.3° C was observed in two cases.

8. INTRAVENTRICULAR PRESSURE

Since the irrigator was hanged up about 80 cm higher than the head-level of animal during the irrigation, the intraventricular pressure should be naturaly elevated. The intraventricular pressure, which was measured on the opposite side of operation during the irrigation, was about 10 cm H_2O less than the height of the column of irrigated fluid. Therefore, the appearance of symptoms due to the rise of intraventricular pressure should be considered, while no severe symptom was encountered in this experiments. However, when irrigated fluid escaped into the subarachnoidal space or infiltrated into the brain matter on account of inadequate procedure of the irrigation, following symptoms were observed : exophthalmus, rise of intraocular pressure, oculomoter palsy, severe salivation, rigidity of muscles, coma and convulsion.

9. INCIDENTS

No case showed severe incident except for the apnoea, which was observed only in such cases irrigated too vigourously. In five cases transient nystagmus took place, in three cases arrythmia, and in two cases hypersalivation, while all these incidents disappeared as soon as the irrigation was ceased. Occasionally fibrous twitches in the face were also observed as well as shivering happened before and after the introduction to unresponsive state.

In the control irrigation with RINGER's solution of body temperature any incident was never occurred.

(2) CONTROL EXPERIMENTS

1. IRRIGATION WITH RINGER'S SOLUTION OF BODY TEMPERATURE

Under the same conditions above mentioned, the irrigation was performed with RINGER's solution being warmed at 36° C to 39° C on eight dogs, and the unresponsiveness to external stimuli was not resulted in all cases: i. e. nose pinching response and the blinking reflex were not utterly changed, while the reduction and enlargement of pupils on the opposite side of operation in each one case, slight weakening of light reflex in two cases, reduction of respiration and puls rate in one case, and slight relaxation of muscle tonus in one case were observed without any other remarkable incidents (Table 2, Fig. 6, 9 & 10).

2. IRRIGATION WITH HOT RINGER'S SOLUTION

The irrigation with RINGER's solution being warmed at 43° C to 47° C was performed by the same way on four dogs in five times. Diminution of the facial refrexes (nose pinching, blinking, corneal, and light reflex) was scarcely observed. Only in each one case the weakening of blinking and light reflex was noted. Pupils were enlarged in two of them, while in the remaining three cases they were not altered. In all of them muscle tonus was utterly unchanged, while slight acceleration and cessation of respiration were observed in each one case. In this case of respiratory cessation the temperature of outflowed fluid reached at 41° C, being maximal grade in this series. Changes in the pulse rate were irregular : in three cases reduced, in two increased, and in one unchanged. Significant changes in the blood perssure were not observed, while in only one case of respiratory cessation the elevation of blood pressure was occurred probably because of anoxia (Table 3 & Fig. 11).

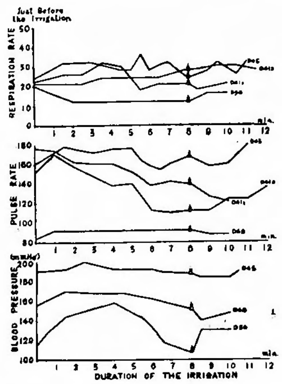

Fig. 11 Traces in the respiration rate, pulse rate and blood pressure during the ventricular irrigation with hot RINGER's solution. The circles with arrows indicate the stopping points of the irrigation.

(3) IRRIGATION WITH PHYSIOLOGICAL SALINE SOLUTION

1. COOLING IRRIGATION

Eight cooling irrigations with physiological saline solution were performed on seven dogs under same conditions with the results differed from those with RINGER's solution : i. e. the nose pinching response was abolished almost always, while disappearance of blinking reflex in five of eight cases, mydriasis in five of seven cases, in three cases the acceleration of respiration and the increase of puls rate in each one and tendency to rigidity or unchanged tonus of the muscles were observed. Delay of recovery from the induced unresponsiveness and considerably severe incidents such as gross shivering, oculomoter palsy, nystagmus, hypersalivation, and convulsion were also observed during or after the irrigation (Table 4).

2. CONTROL : IRRIGATION WITH WARM PHYSIOLOGICAL SALINE SOLUTION

Seven control irrigations with saline solution being warmed at 34° C to 38° C were carried out on seven dogs. In three cases of this series the nose pinching response was abolished, and weakened in one case. Tendency to mydriasis and increase of respiration and pulse rate were observed in the most of cases, while muscle tonus tended to relaxation or stiffness in four cases. Considerable incidents were observed in almost all cases, though in the slightest degree (Table 5).

(4) SURVIVAL TEST

Ten of all 15 dogs being irrigated with Ringer's solution survived. Out of the remaining five dogs, one was sacrificed to obtain the specimen of the brain matter, while one died soon after the stabbing of the medulla with a tip of thermocouple. Two of the other three dogs succumbed to apnoea caused by the excessive cooling, and one died from meningitis after the experiment.

Survived dogs showed no ataxia excepting the ones which were stabbed in the vermis of cerebellum, and restored well to walk on the following or next day. In some of them the disturbance of vision took place because of the destruction of the brain in the procedure of intubation or papilledema during and after the irrigation, while they were ameliorated within several days.

Any significant abnormality or disturbance in function, which might be considered to be due to the cooling irrigation, was not observed. One of the irrigated female dogs became pregnant after a month of the experiment, gave birth and bred pups as well as the other normal dogs. Concerning the change of charactor, details of which were impossible to be estimated, while violent dogs tended to become more gentle for a long time after the experiment.

DISCUSSION

For many years physiological reactions of the living bodies under hypothermic circumstances have been pathophysiologically studied by many investigators, especially in Japan Yanagi reported in 1943, during the second world war, the detailed investigation of "Hypothermia and Living Bodies", in which it was showed that, when the living body was exposed under the hypothermia untill rectal temperature being decreased beneath the range of 30° C, all physiological functions and metabolisms were declined progressively, and gradually froze to death. [19] But the purpose of his investigation was the protection for death from cold, mainly from the standpoint of military medicine.

Since the initiation of "Hibernation anesthesia" by Laborit and Huguenard in 1951 [8] a clinical application of artificial hypothermia has been strikingly developped under the employment on the cardiac surgery. In 1954, a new methods of this anesthesia were reported by SAKAKIBARA [12] KIMOTO [6] and PARKINS [11] in which the brain was cooled from outside or perfused with the cooled blood for the protection of the cerebral cortex from anoxia in consequence of the lowering of oxygen consumption in it.

According to them it was assertained that all of physiological conditions in the living body so reduced by their procedures when the cerebral temperature was lowered at 15° C to 20° C, corresponding as same grade as the condition at 30° C of rectal temperature following general hypothermia. From this view point in a local hypothermia of the central nervous system, our experiments on the cooling irrigation of cerebral ventricular system were attempted to cool the thin layer of the nervous tissues closely beneath the internal wall of cerebral ventricles, which has more important functions than the cerebral cortex for the maintenance of life, and to investigate the changes in the nervous functions following the irrigation. It may be of importance what a kind of physiological change is brought out under the cooling of the nervous tissues particularly of the thalamus, hypothalamus, periaqueductal tissue and the floor of fourth ventricle. In this experiment, the cooled area was only the thin layer contact with the ventricular wall, and it never took place the cortical hypothermia, since in the brain matter the prompt mediation of hypothermia may be considerably disturbed because of the ceaseless warm blood supply in it.

The cooling irrigation of cerebral ventricles, which brings the consummate reversible rapid unresponsiveness, has no incident during short period, and leaves no functional disturbance so far as the irrigation is performed not so long. Occasionally observed temporary symptoms are seemed to be due to acute cerebral edema owing to salt-action of fluid, while RINGER's solution was employed as the most resembling solution with cerebrospinal fluid. Such incidents as mydriasis, hypersalivation, acceleration of respiration, arrythmia, rigidity of muscles, convulsion, nystagmus, oculomotor palsy, and exopthalmus were observed more frequently in the experiments with use of physiological saline solution than those of RINGER's solution. This discrepancy may be due to the pharmacologically different effects of both fluids against the nervous tissue.

It has been confirmed that the excitability of nervous cells increases when sodium ion abundantly invades into the cells and intracellural pottasium ion is driven out. If a large amount of isotonic saline solution containing larger amount of sodium ion than cerebrospinal fluid comes into contact with the internal wall of cerebral ventricles, sodium ion accumulates so much in the cells that the central nervous cells are dehydrated, causing the accumlation of water in the brain matter. Consequently, these changes provoke severe incidents. Recently, HAYASHI reported that the irrigation in the cerebrospinal space with isotonic saline solution caused convulsion and he named this phenomenon "salt discharge of nerve cell" [5]. Likewise in our present experiment convulsions were observed on several cases being irrigated with physioligical saline solution, while their frequency was not so much probably because of the brief irrigating duration.

When Ringer's solution was employed, on the contrary, the incidents seldom occurred and recovered quickly if happened, possibly from the reason that pottasium ion in the Ringer's solution has an action of declining the reflex-excitability, and calcium ion has a cramp-inhibiting effect [10] Therefore at present the Ringer's solution may be suitable for the purpose of use in this experiment, but we are intending to use the more ideal solution, of which composition is more similar to that of cerebrospinal fluid.

Concerning the loss of consciousness which is a principal subject in this experiment, estimation is made by the use of the reactions of escape-reflexes for irritation of pain and touch from out-side, having consideration for the difficulty of the estimation on the state of consciousness in animals. Above all, "nose pinching test" may be a sharp and simple method for this purpose, observing that the nose pinching response abolishes first in the adequately performed cooling irrigation before the disappearance of blinking, corneal and light reflexes.

With the consideration of the fact that the changes of pupils are closely related with the tension of autonomous nerves, of which centers existing in the medulla oblongata, being effected directly by the cooling irrigation of the cerebral ventricles, the changes of pupils may be a key point to understand the essential mechanism of this experiment. From the pharmacological standpoint, it may be due to the difference of salt action between both fluids that the size of pupils is reduced in the cooling irrigation with use of Ringer's solution (Table 1) and enlarged with physiological saline solution (Table 5). In ahort, it may be assumed that mydriasis takes place on account of the effect of sodium ion to the center of whether sympathetic or parasymapathetic nerves. On the other hand, myosis observed in the cooling irrigation with Ringer's solution may be merely due to the cooling effect, because of that the changes on size of pupils were hardly confirmed in our control experiments with warm Ringer's solution. The mechanism of changes on pupils could not verified in this experiment, however such assumption is available that myosis in the cooling irrigation with Ringer's solution may be not a result of parasympathetic stimulation from the fact that light reflex, of which center exists in the oculomotor nucleus, is seldom effected by the cooling irrigation.

Judging from the results of control experiments, changes in respiration, pulse, and blood pressure are also thought to be due to the effects of cooling to the respiratory and vasomotoric center.

There is a well known principle, that the nerve is first excited and later paralysed by various stimuli. In our cooling irrigation the activity of nervous centers may be reduced reversibly after being activated. In addition, from the results of control experiment with hot fluid, it was apparent that these remarkable effects were merely due to the influence of cold among the thermal stresses, since hot Ringer's solution hardly introduced such depressing effect.

From the fact that the appearance of the changes of respiration rate is more remarkable and rapid than those of pulse and blood pressure, the cooling may effect first to the respiratory center, and in this stage cardiac function is intensed consequently with increased cardiac output. These relation between respiration and blood pressure are confirmed by the fact that in dogs which fell into apnoea the blood pressure was elevated due to the insufficiency of oxygen, and lowered gradually after the sufficient supply of oxygen as shown in Fig. 8.

For the performance of the effective cooling irrigation without incident for longer duration, the following notions should be remained in mind : (1) Irrigating fluid should have a same composition and osmotic pressure to be compared with cerebrospinal fluid in order to prevent cerebral edema. (2) Oxygen supply should be sufficient in order to prevent the incident due to anoxia, as the respiratory center is the weakest under the cooling irrigation. (3) Cooling effect should not be excess, excepting the case managed with artificial respiration.

SUMMARY

On adult mongrel dogs it was confirmed that the cooling irrigation of the cerebral ventricular system with cold Ringer's solution (from the lateral ventricle on one side to the major cisterna, through the third ventricle, aqueduct of Sylvius and fourth ventricle) caused the reversible unresponsiveness to external stimuli.

Under the suitable conditions of this irrigation (temperature of inflowing fluid: about 8° C, outflowed fluid : about 22° C, rate of irrigation : ca. 30cc per minute) dogs became unresponsive to the external stimuli after about 10～30 seconds from the beginning of irrigation, and in the course of irrigation the respiration became to be slow and deep with tendency of slight bradycardia, and any convulsive seizure was not observed, while blood pressure was lowered decidedly following the slight initial elevation and rectal temperature remained to be unchanged throughout.

With lapse of 10～30 seconds after the cessation of irrigation, dogs returned completely to the state aforegoing, and aquired none of remarkable pathological signs.

In the control experiments dogs irrigated with warm Ringer's solution of body temperature under the same conditions did not show such unresponsive state as mentioned above. This was the same with hot Ringer's solution, while in the use of physiological saline solution convulsion and other harmful pathological signs were recognized.

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和文抄録

脳室灌流冷却に関する研究 第1篇

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体重4～12.5kgの成犬を使用して，一側の側脳室から第3脳室，中脳水道，第4脳室を経て大槽に至る間の脳室系を冷リンゲル氏液を以て灌流冷却する実験を行い，適当な条件の下に行つた灌流冷却では，動物は速やかに外界からの刺戟に対する反応を消失し，灌流冷却を停止すると，再び速やかに刺戟に対する反応が恢復するという成績を得た.

この様な反応の消失を来すための至適条件は，流入液温約8℃，流出液温約22℃，灌流速度毎分約30ccであつた．実験操作の便宜上，準備手術に先だつてラボナールの軽麻酔を行い，その覚醒を待つて灌流冷却を行つたが，対照として全くラボナールを用いなかつた例に於ても，実験成績は殆んど同一であつた.

動物の意識の状態の判定には，吾々の創案による「鼻つまみ反応」及びその他の顔面諸反射によつたが，上記の条件内の実験では，全例に平均40秒以内に鼻つまみ反応の消失又は減弱を認めた．その他，呼吸数，脈搏数，血圧，髄液圧，直腸温をも灌流冷却の経過中及びその前後に於て観察したが，呼吸数は灌流冷却の経過に応じて著明に減少し，呼吸停止を来したものも数例あつた．脈搏数及び血圧も夫々減少，低下する傾向が認められた．しかしこれらの変化は灌流停止後速やかに恢復し，鼻つまみ反応及び諸反射は約30秒以内，呼吸・脈搏・血圧は2～3分以内に恢復して灌流前の状態に戻つた．髄液圧は灌流液圧より10cm低い圧を認め，直腸温には著変は認められなかつた。

対照実験として，高温及び体温リンゲル氏液と，冷・温両生理的食塩水による同一経路の灌流を行つたが，加温リンゲルの場合は何れも刺戟に対する反応を消失したり，呼吸・脈搏・血圧に著変を来す様なことはなかつた.

生食水の場合には，痙攣その他の副作用を来す例が多かつた.

この様なリンゲル氏液による灌流冷却では，灌流による重篤な副作用を来したものはなく，術后の一般状態の恢復後も神経学的な機能の異常などを認めなかつた.

以上の実験成績から，本実験によつて起る意識の障碍は低温の作用によるもので，髄液圧の亢進や，脳室壁に対する機械的衝撃によるものではないと考えられる.